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(54) Title: USE OF ALLICIN FOR CONTROL OF WEIGHT IN MAMMALS

(57) Abstract: Allicin is used for control of weight in mammals, in particular for reduction of weight and/or prevention of weight gain, more particularly for prevention of weight gain in an individual who has previously undergone a diet for reducing weight.

USE OF ALLICIN FOR CONTROL OF WEIGHT IN MAMMALS

FIELD OF THE INVENTION

The present invention relates to compositions comprising allicin and to methods for reduction of weight and/or for prevention of weight gain in mammals, particularly in humans.

BACKGROUND OF THE INVENTION

Garlic and garlic preparations commercially available in the form of garlic oil, extracts, pills or tablets are widely used for some therapeutic purposes including lowering blood pressure, although their therapeutic effect is still questionable. Usually the preparation procedures of such garlic preparations are unknown and the composition and amount of their active ingredients are not defined making difficult the proper evaluation of their therapeutic effect. Nevertheless, some studies reported the beneficial effects of garlic on cardiovascular risk factors, mainly hyperlipidemia and thrombogenesis in animals and in humans. Thus, administration of fresh garlic or etheric garlic extracts was shown to induce an increase in fibrinolytic activity (Bordia et al., 1977; Kieswetter et al., 1990), to inhibit platelet aggregation (Makheja and Bailey, 1990), to protect cholesterol-fed rabbits against the onset of atherosclerosis (Efendy et al., 1997), and to improve lipid profile including reduction of serum cholesterol levels (Bordia and Verma, 1980; Bordia et al., 1975; Knipschild and Ter-Riet, 1989; Augusti and Mathew, 1974). These studies demonstrated a very impressive effect of garlic, but most studies were limited by several factors such as lack of controlled methods and suitable double-blind studies and use of preparations with unknown amount and chemical identification of the active ingredient.

Among the active principles present in garlic, the principal component is allicin (thio-2-propene-1-sulfinic acid S-allyl ester), a chemically unstable,

colorless liquid that is thought to be responsible for both the odor and much of the biological activity of garlic. Allicin is not present as such in the intact garlic clove, but is produced together with pyruvate and ammonia from the odorless precursor alliin (+)(S-allyl-L-cysteine sulfoxide) in the presence of the enzyme alliinase [E.C. 4.4.1.4.]. Alliin and alliinase are found in different compartments of the garlic clove. The cutting or crushing of the clove enables the enzyme to come into contact with the precursor thus producing allicin.

Allicin was shown to exhibit the beneficial properties ascribed to garlic (Eilat et al., 1995; Elkayam et al., 1999) but its use as the active ingredient of pharmaceutical compositions has not been made possible for lack of suitable methods for its production in stable and purified form. The chemical synthesis involves many steps and is complicated, laborious, expensive, and very inefficient.

The enzymatic method for the preparation of allicin is more attractive. However, alliinase is a so-called "suicidal enzyme", that is rapidly and irreversibly inactivated by its own reaction product, allicin. Thus, incubation for a few minutes of alliinase with the substrate alliin or its product, allicin, leads to a biologically inactive enzyme after one or a very limited number of cycles. This problem has recently been solved by the inventors by the method described in PCT Publication No. WO 97/39115 (Mirelman et al., 1997), whereby continuous production of substantially pure allicin is provided by adding the substrate alliin to a column comprising immobilized garlic alliinase.

SUMMARY OF THE INVENTION

It has now been found, according to the present invention, that allicin is also effective in control of weight in mammals.

The present invention thus relates to compositions comprising allicin for control of weight in mammals, both for human and veterinary use. In particular, the invention provides pharmaceutical compositions for reduction of weight and/or prevention of weight gain in humans, and more particularly in individuals which have undergone a diet for reducing weight.

The pharmaceutical composition of the invention may be presented in any suitable form of administration as well known for the artisans in the art, Preferably, the composition is in a form for oral administration, for example, an aqueous solution of allicin or allicin adsorbed in a pharmaceutically acceptable polymer, e.g. a natural polysaccharide such as, but not being limited to, cellulose, starch, dextran, agar, agarose, alginic acid, guar and the like. These compositions may be prepared by mixing and spray drying the ingredients and incorporating the resulting powder into capsules by standard techniques.

The amounts of allicin to be used according to the invention will depend on the individual to be treated - the sex and age of the patient, his/her health condition and weight before treatment, and can be easily determined by physicians as necessary.

Alternatively, the composition may be in the form of a prodrug consisting of suitable forms of alliin and alliinase that will produce allicin in situ after ingestion. The alliinase, natural or recombinant, may be in soluble or insoluble form, for example, it may be chemically, physically or biologically immobilized on a solid support as described in published PCT Publication No. WO 97/39115, herein incorporated by reference as if fully described herein. In one preferred embodiment, alliinase is chemically coupled to Cl-Sepharose as described in WO 97/39115.

In another aspect, the invention relates to the use of allicin for the preparation of a pharmaceutical composition for reduction of weight and/or prevention of weight gain.

In still another aspect, the invention relates to a method for reduction of weight and/or prevention of weight gain which comprises administering to an individual in need thereof an effective amount of allicin.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the average body weight of 8 rats, initially and after receiving fructose diet for 3 and 5 weeks.

Fig. 2 shows the average body weight of 7 rats, initially and after receiving fructose diet for 3 weeks and then fructose + allicin (8 mg/kg/day) for another 2 weeks.

Fig. 3 shows the average body weight of 5 rats, initially and after receiving fructose diet + allicin (8 mg/kg/day) for 3 weeks and then fructose only for another 2 weeks.

Fig. 4 shows the average body weight of 8 rats, initially and after receiving fructose diet for 3 weeks and then fructose + trandolapril (0.1 mg/kg/day) for another 2 weeks.

Fig. 5 shows the average body weight of 10 rats, initially and after receiving fructose diet for 3 weeks and then fructose + enalapril (20 mg/kg/day) for another 2 weeks.

DETAILED DESCRIPTION OF THE INVENTION

The invention will be illustrated according to the following non-limiting Example with reference to the drawings.

EXAMPLE. Allicin prevents weight gain in rats on a fructose-enriched diet

Materials and Methods

(a) Pure allicin was produced by interaction of the synthetic substrate alliin with purified alliinase isolated from garlic cloves as described previously in PCT Publication No. WO 97/39115 (Mirelman et al., 1997). Fructose was purchased from Harlan, Teklad (Madison, WI, USA). Sprague-Dawley rats were purchased from ANILAB, Tal-Shahar, Israel.

(b) Experiments were carried out on Reaven's rat model, according to which Sprague-Dawley rats become insulin-resistant, hyperinsulinemic, hypertriglyceridemic and hypertensive when fed a fructose-enriched diet (Reaven, 1991). This model was previously used by the inventors to test the effect of different angiotensin-converting enzyme inhibitors (ACEI), namely enalapril,

ramipril and lisinopril, on metabolic parameters and hypertension in said rats, and enalapril was found to have the most beneficial effect on all parameters (Erlich and Rosenthal, 1995).

Experimental

Male Sprague-Dawley rats, 8 per group, initially weighing 240-250 g, were fed a fructose-enriched diet which consisted of 21% protein, 5% fat, 60% carbohydrate, 0.49% sodium and 0.49% potassium, for 5 weeks, which produced hyperinsulinemia, hypertension and hypertriglyceridemia.

Animals were divided into 5 groups:

I. Fructose only (control group).

II. Allicin (8mg/kg/day) added daily during the last 2 weeks.

III. Allicin (8mg/kg/day) given during the first 3 weeks of fructose-rich diet.

IV. Trandolapril (0.1mg/kg/day) added during the last 2 weeks.

V. Enalapril (20mg/kg/day) added during the last 2 weeks.

Both trandolapril and enalapril are known ACEI inhibitors used for treatment of arterial hypertension.

Weight was measured at the beginning of the experiment and after 3 and 5 weeks on the diet. The same amount of food was consumed by all 5 study groups.

As shown in Fig. 1, rats on a diet of fructose only (group I, 8 rats – control group) had their weight raised from 233.5±8.0 g to 329.6±28.8 g after 3 weeks, and at the end of 5 weeks to 376.1±38.4 g.

As shown in Fig. 2, rats after a 3-week fructose-enriched diet had their weight raised from 259.1±9.6 g to 292.2±12.6 g, and their weight remained fairly steady when administered fructose+allicin during the following 2 weeks (group II, 7 rats), reaching 282.4±17.4 g.

When the protocol was reversed and the animals were given fructose and allicin concomitantly for 3 weeks and then fructose alone for another 2 weeks (group III, 5 rats), their weight remained steady: 262.2±18.4 g at baseline,

273±14.7 g after 3 weeks on fructose/allicin and 263±24.2 g after 2 more weeks on fructose alone (Fig. 3).

As shown in Fig. 4, rats that received a fructose-enriched diet for 3 weeks had their weight raised from 229.8±3.8 g at the baseline to 330.2±15.5 g after 3 weeks, and then after receiving fructose + trandolapril group (group IV, 8 rats) for another 2 weeks had their weight raised to 355.1±20.0 g at the end of the 5th week. Similar results were obtained with rats fed fructose for 3 weeks and then fructose + enalapril group (group V, 10 rats) for another 2 weeks (Fig. 5).

The results above clearly show that both the control and trandolapril/enalapril groups continued to gain weight (Figs. 1, 4, 5), while the allicin groups did not (Figs. 2, 3).

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CLAIMS:

1. A pharmaceutical composition for control of weight in mammals comprising allicin and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1, for reduction of weight.

3. The pharmaceutical composition according to claim 1, for prevention of weight gain.

4. The pharmaceutical composition according to claim 3, for prevention of weight gain in individuals which have undergone a diet for reducing weight.

5. The pharmaceutical composition according to any one of claims 1 to 4, for oral administration.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein allicin is provided in the form of a prodrug consisting of suitable forms of alliin and alliinase.

7. The pharmaceutical composition according to claim 6, wherein the alliinase is immobilized on a solid support.

8. Use of allicin for the preparation of a pharmaceutical composition for control of weight in mammals.

9. The use according to claim 8, for reduction of weight.

10. The use according to claim 8, for prevention of weight gain.

11. The use according to claim 10, wherein said pharmaceutical composition is for prevention of weight gain in individuals which have undergone a diet for reducing weight.

12. The use according to any one of claims 8 to 11, wherein the composition is for oral administration.

13. The use according to any one of claims 8 to 11, wherein allicin is provided in the form of a prodrug consisting of suitable forms of alliin and alliinase.

14. The use according to claim 13, wherein the alliinase is immobilized on a solid support.

15. A method for controlling weight which comprises administering to an individual in need thereof an effective amount of allicin.

16. A method according to claim 15 wherein allicin is administered for reduction of weight gain.

17. A method according to claim 15 wherein allicin is administered for prevention of weight gain.

18. The method according to claim 17, for prevention of weight gain in an individual who has previously undergone a diet for reducing weight.

19. The method according to any one of claims 15 to 18, wherein allicin is administered orally.

20. The method according to any one of claims 15 to 19, wherein allicin is provided in the form of a prodrug consisting of suitable forms of alliin and alliinase.

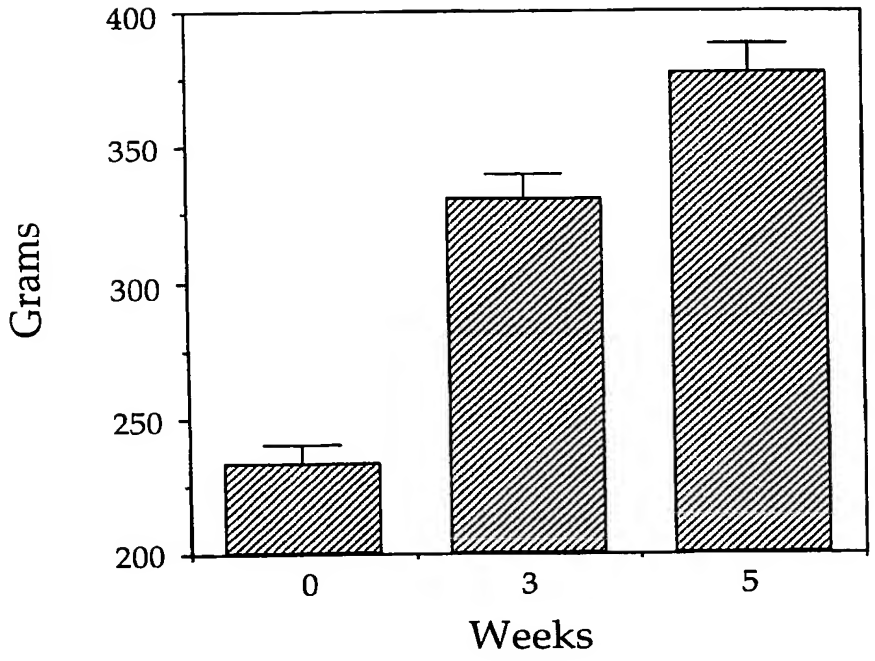

Fig. 1

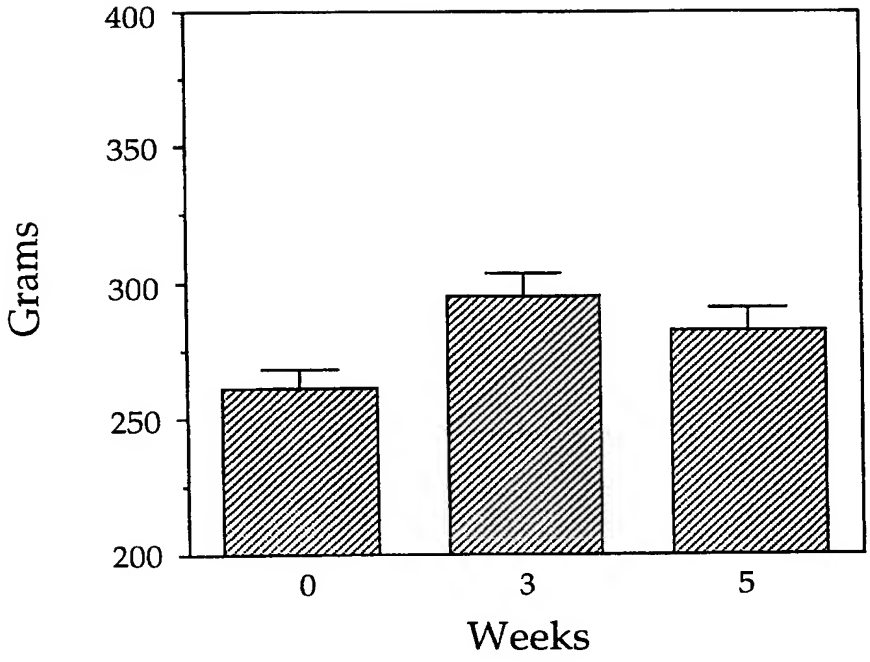

Fig. 2

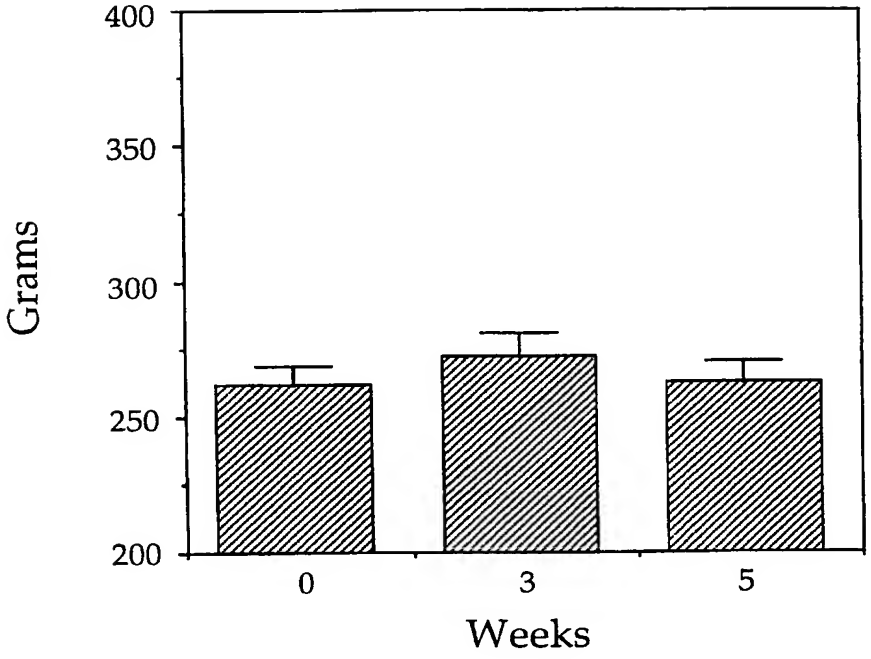

Fig. 3

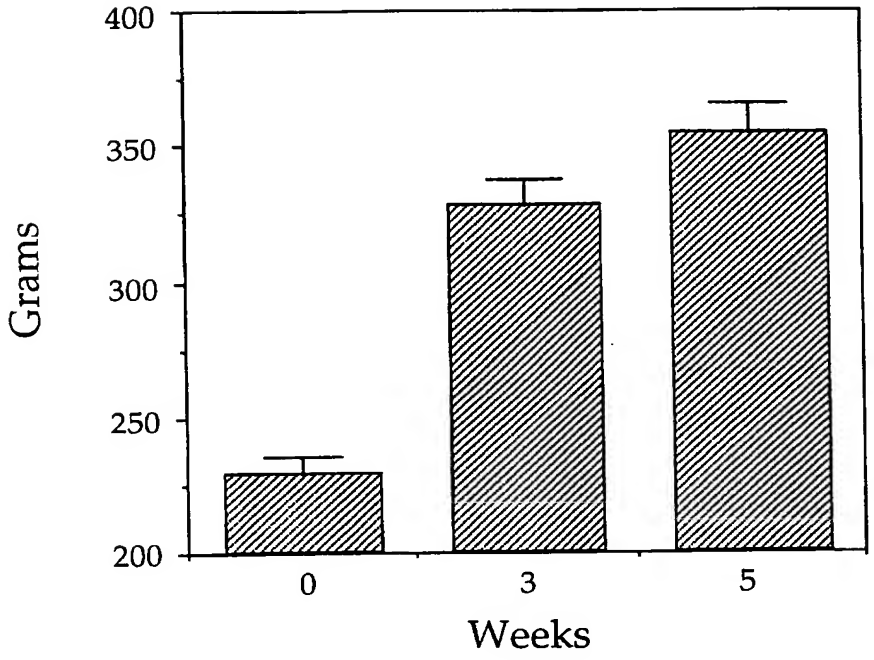

Fig. 4

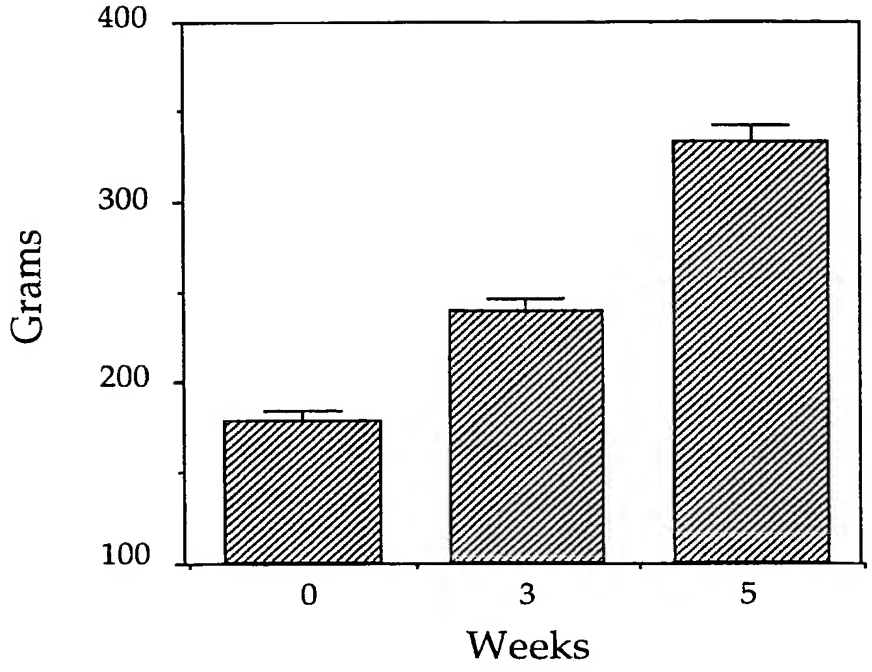

Fig. 5

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WO 00/74663 A3

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/IL 00/00323

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/255 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOON SHIK LEE : "A comparative study of the effect of allicin and arsenite on albino rats with special regard to the effect on body weight, hemoglobin, and hepatic histology" NEW MEDICAL JOURNAL, no. 1, 1967, pages 99-101, XP000983088 seoul, korea page 100, line 1 - line 5 ---	1,8,15
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2001	22/02/2001

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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